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(54) ANGIOSTATIC AGENTS AND COMPOSITIONS FOR TREATING GLC1A GLAUCOMA

ANGIOSTATISCHE VERBINDUNGEN UND ZUSAMMENSETZUNGEN ZUR BEHANDLUNG DES GLC1A GLAUKOMS

AGENTS ANGIOSTATIQUES ET COMPOSITIONS POUR LE TRAITEMENT DU GLC1A GLAUCOME

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(56) References cited:

WO-A-91/19731	**WO-A-93/10141**
WO-A-95/18621	**US-A- 4 876 250**
US-A- 5 371 078	**US-A- 5 698 545**

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Description

Background of the Invention

Field of the Invention

[0001] This invention is directed to the use of angiostatic agents for the manufacture of a medicament treating glaucoma or ocular hypertension resulting from altered expression of the GLC1A gene (hereinafter GLC1A or 1q glaucoma) in an individual.

Description of Related Art

[0002] The glaucomas are a heterogeneous group of optic neuropathies characterized by cupping of the optic nerve head, thinning of the retinal nerve fiber layer due to loss of retinal ganglion cells, and specific pathognomonic changes in visual fields. Elevated intraocular pressure (IOP) is a very important risk factor for the development of most common forms of glaucoma (Sommer A, et al., "Relationship Between Intraocular Pressure and Primary Open Angle Glaucoma Among White and Black Americans," *Arch. Ophthalmol.*, 109:1090-1095, (1991)).

[0003] A family history of glaucoma also is an important risk factor for the development of glaucoma. It appears that a significant portion of glaucoma is inherited (or at least the risk for developing glaucoma is inherited) although it is often difficult to establish clear inheritance patterns for most of the glaucomas because of the disease onset late in life and the slowly progressive clinical manifestations of the disease. Despite these problems, a number of families with heritable forms of glaucoma have been identified and these families have been used to map a variety of glaucoma genes (Sheffield, et al., "Genetic Linkage of Familial Open Angle Glaucoma to Chromosome 1q21-q31," *Nature Genetics,* 4:47-50 (1993); Sarfarazi, et al., "Assignment of a Locus (GLC3A) for Primary Congenital Glaucoma (Buphthalmos) to 2p21 and Evidence for Genetic Heterogeneity," *Genomics,* 30:171-177 (1995); Akarsu, et al., "A Second Locus (GLC3B) for Primary Congenital Glaucoma (Buphthalmos) Maps to the 1p36 Region," *Human Molecular Genetics,* 5 (8):1199-1203 (1996); Stoilova, et al., "Localization of a Locus (GLC1B) for Adult-Onset Primary Open Angle Glaucoma to the 2cen-q13 Region," *Genomics,* 36:142-150 (1996); Wirtz, et al., "Mapping a Gene for Adult-Onset Primary Open-Angle Glaucoma to Chromosome 3q," *Am. J. Hum. Genet.,* 60:296-304 (1997); Andersen, et al., "A Gene Responsible for the Pigment Dispersion Syndrome Maps to Chromosome 7q35-q36," *Arch. Ophthalmol.*, 115:384-388 (1997). The first glaucoma gene mapped (GLC1A) was in a large family with autosomal dominant inherited juvenile glaucoma (JG). This disease is characterized by an early disease onset (late teens to early 20s), relatively high IOPs, and general resistance to conventional pharmacological IOP lowering therapy. The GLC1A gene was mapped by positional cloning and linkage analysis to chromosome 1q22-q25 (Sheffield et al, *Id.),* and a number of other groups have confirmed the 1q location of this juvenile glaucoma gene (Richards, et al., "Mapping of a Gene for Autosomal Dominant Juvenile-Onset Open-Angle Glaucoma to Chromosome 1q," *Am. J. Hum. Genet.,* 54:62-70 (1994); Morissette, et al., "A Common Gene for Juvenile and Adult-Onset Primary Open-Angle Glaucomas Confined on Chromosome 1q," *Am. J. Hum. Genet.,* 56:1431-1442 (1995); Wiggs, et al., "Genetic Linkage of Autosomal Dominant Juvenile Glaucoma to 1q21-q31 in Three Affected Pedigrees," *Genomics,* 21:299-303 (1994); Meyer, et al., "Age-Dependent Penetrance and Mapping of the Locus for Juvenile and Early-Onset Open-Angle Glaucoma on Chromosome 1q (GLC1A) in a French Family," *Hum. Genet.*, 98:567-571 (1996); Graff, et al., "Confirmation of Linkage to 1q21-31 in a Danish Autosomal Dominant Juvenile-Onset Glaucoma Family and Evidence of Genetic Heterogeneity," *Hum. Genet.*, 96:285-289 (1995). Glaucoma due to the GLC1A gene is often referred to as 1q glaucoma.

[0004] The GLC1A gene was identified as encoding a 57 kD protein expressed in the trabecular meshwork (TM) (Stone, et al., "Identification of a Gene That Causes Primary Open Angle Glaucoma," *Science,* 275:668-670 (1997). The expression of the GLC1A gene, and the encoded TM protein, is up-regulated by glucocorticoids (Polansky, et al., "Eicosanoid Production and Glucocorticoid Regulatory Mechanisms in Cultured Human Trabecular Meshwork Cells," *The Ocular Effects of Prostaglandins and Other Eicosanoids,* pp. 113-138 (1989); Polansky, et al., "*In Vitro* Correlates of Glucocorticoid Effects on Intraocular Pressure," *Glaucoma Update IV* (1991); and Polansky, et al., "Cellular Pharmacology and Molecular Biology of the Trabecular Meshwork Inducible Glucocorticoid Response Gene Product," *Ophthalmologica,* 211:126-139 (1997)). This TM protein is also known as TIGR (trabecular meshwork inducible glucocorticoid response) (Polansky, *Id.).* The glucocorticoid-induction of this TM protein has been suggested to be involved in the generation of glucocorticoid-induced ocular hypertension and glaucoma (Polansky, *Id.*).

[0005] The GLC1A gene is expressed in other ocular tissues such as the ciliary epithelium (Ortego, et al., "Cloning and Characterization of Subtracted cDNAs from a Human Ciliary Body Library Encoding TIGR, a Protein Involved in Juvenile Open Angle Glaucoma with Homology to Myosin and Olfactomedin," *FEBS Letters,* 413:349-353 (1997)) and the retina (Kubota, et al., "A Novel Myosin-like Protein (Myocilin) Expressed in the Connecting Cilium of the Photoreceptor: Molecular Cloning, Tissue Expression, and Chromosomal Mapping," *Genomics,* 41:360-369 (1997)). The gene

is referred to by several name[illegible]uding GLC1A (Sheffield, *supra;* Sunden, et al[illegible]e Mapping of the Autosomal Dominant Juvenile Open Angle Glaucoma (GLC1A) Region and Evaluation of Candidate Genes," *Genome Research,* 6:862-869 (1996); Stone, et al., *supra*), TIGR (Polansky *supra;* Ortego, *supra),* and myocilin (Kubota, *supra).* Mutations GLC1A are not only responsible for juvenile glaucoma, but also a significant subset of adult onset primary open angle glaucoma (Stone, et al., *supra;* Adam, et al., "Recurrent Mutations in a Single Exon Encoding the Evolutionarily Conserved Olfactomedin-Homology Domain of TIGR in Familial Open-Angle Glaucoma," *Human Molecular Genetics,* 6 (12):2091-2097 (1997)). The 1q glaucoma gene (GLC1A, TIGR) is the subject of Nguyen, et al., U.S. Patent No. 5,606,043, issued February 25, 1997.

[0006] Glucocorticoids have been associated with the development of ocular hypertension and primary open angle glaucoma (Kass, et al., "Corticosteroid-Induced Glaucoma, In Ritch, R., Shields, M. B., Krupin, T. (eds.)," *The Glaucomas,* The C. V. Mosby Company, St. Louis, MO, pp. 1161-1168 (1989); DeSantis, et al., "Dexamethasone-Induction of Ocular Hypertension in the Primate, *ARVO Abstracts. Invest. Ophthalmol. Vis. Sci.,* 31(Suppl.):99 (1990); Knepper, et al., "Intraocular Pressure and Glycosaminoglycan Distribution in the Rabbit Eye: Effect of Age and Dexamethasone," *Exp. Eye Res.*, 27: 567-575 (1978); Francois, et al., "Ultrastructural and Morphometric Study of Corticosteroid Glaucoma in Rabbits, *Ophthalmic Res.*, 16:168-178 (1984); Lorenzetti, O. J., "Effects of Corticosteroids on Ocular Dynamics in Rabbits," *J. Pharmacol. Exp. Therap.,* 175:763-772 (1970); and Zhan, et al., "Steroid Glaucoma: Corticosteroid-Induce Ocular Hypertension in Cats," *Exp. Eye Res.*, 54:211-218 (1992)). Glaucoma patients have also been reported to have higher levels of the endogenous glucocorticoid, cortisol (Rozsival, et al., "Aqueous Humour and Plasma Cortisol Levels in Glaucoma and Cataract Patients," *Current Eye Research,* 1:391-396 (1981); Ray, et al., "Plasma Cortisol in Glaucoma," *Ann. Ophthalmol.*, 9:1151-1154 (1977); and Schwartz, et al., "Increased Plasma Free Cortisol in Ocular Hypertension and Open Angle Glaucoma," *Arch. Ophthalmol.,* 105:1060-1065 (1987)).

[0007] It is known that trabecular meshwork cells have glucocorticoid receptors and that glucocorticoid binding with these receptors causes a change in trabecular meshwork cell gene expression. Known manifestations of this change include a reorganization of the cytoskeleton (Wilson, et al., "Dexamethasone Induced Ultrastructural Changes in Cultured Human Trabecular Meshwork Cells, *Cur. Eye Res.,* 12:783-793 (1993), and Clark, et al., "Glucocorticoid-Induced Formation of Cross-Linked Actin Networks in Cultured Human Trabecular Meshwork Cells," *Invest. Ophthalmol. Vis. Sci.,* 35:281-294 (1994)) and increased deposition of the extracellular matrix material in trabecular meshwork cells. As a result, the trabecular meshwork becomes "clogged" and unable to perform one of its most critical functions, that is, serving as a gateway for aqueous humor flow from the anterior chamber of the eye. When the aqueous humor flow out of the eye via the trabecular meshwork is diminished, the intraocular pressure of the eye rises. If this state of elevated intraocular pressure is maintained or frequently occurs, the optic nerve head can be damaged resulting in the loss of visual field. Loss of visual field is the hallmark symptom associated with glaucoma.

[0008] Endogenous glucocorticoids may be responsible for producing the changes in the trabecular meshwork that lead to ocular hypertension and glaucoma.

[0009] In summary, the GLC1A gene product can lead to the development of ocular hypertension and glaucoma in one of two ways: (1) mutations in GLC1A are responsible for most forms of juvenile glaucoma and a subset of adult onset POAG or (2) exposure of some individuals to glucocorticoids leads to increased GLC1A expression in the TM which causes increased aqueous humor outflow resistance and the development of ocular hypertension. The precise mechanism(s) responsible for GLC1A effects on IOP are currently unknown.

[0010] Steroids functioning to inhibit angiogenesis in the presence of heparin or specific heparin fragments are disclosed in Crum, et al., "A New Class of Steroids Inhibits Angiogenesis in the Presence of Heparin or a Heparin Fragment," *Science,* 230:1375-1378 (December 20, 1985). The authors refer to such steroids as "angiostatic" steroids. Included within the new class of steroids found to be angiostatic are the dihydro and tetrahydro metabolites of cortisol and cortexolone. In a follow-up study directed to testing a hypothesis as to the mechanism by which the steroids inhibit angiogenesis, it was shown that heparin/angiostatic steroid compositions cause dissolution of the basement membrane scaffolding to which anchorage dependent endothelia are attached resulting in capillary involution; see, Ingber, et al., "A Possible Mechanism for Inhibition of Angiogenesis by Angiostatic Steroids: Induction of Capillary Basement Membrane Dissolution," *Endocrinology,* 119:1768-1775 (1986).

[0011] A group of tetrahydro steroids useful in inhibiting angiogenesis is disclosed in International Patent Application No. PCT/US86/02189 (WO 87/02672), Aristoff, et al., (The Upjohn Company). The compounds are disclosed for use in treating head trauma, spinal trauma, septic or traumatic shock, stroke and hemorrhage shock. In addition, the patent application discusses the utility of these compounds in embryo implantation and in the treatment of cancer, arthritis and arteriosclerosis. The compounds are not disclosed for ophthalmic use.

[0012] Tetrahydrocortisol (THF) has been disclosed for its use in lowering the intraocular pressure (IOP) of rabbits made hypertensive with dexamethasone alone, or with dexamethasone/5-beta-dihydrocortisol; see Southren, et al., "Intraocular Hypotensive Effect of a Topically Applied Cortisol Metabolite: 3-alpha, 5-beta-tetrahydrocortisol," *Investigative Ophthalmology and Visual Science,* 28 (May, 1987). The authors suggest THF may be useful as an antiglaucoma agent. In U.S. Patent No. 4,863,912, issued to Southren et al. on September 5, 1989, pharmaceutical compositions

containing THF and a method of using these compositions to control intraocular pressure are disclosed. THF has been disclosed as an angiostatic steroid in Folkman, et al., "Angiostatic Steroids," *Ann. Surg.*, 206(3) (1987) wherein it is suggested angiostatic steroids may have potential use for diseases dominated by abnormal neovascularization, including diabetic retinopathy, neovascular glaucoma and retrolental fibroplasia.

[0013] US-Patent Nos. 5,371,078, 5,698,545 and 4,876,250 and WO 93/10141 disclose angiostatic steroids for use in controlling ocular hypertension as well as pharmaceutical compositions of these angiostatic steroids and methods for their use in treating ocular hypertension, including controlling the ocular hypertension associated with primary open angle glaucoma. None of these documents discloses that an angiostatic agent is useful in treating GLC1A glaucoma.

[0014] Steroids which inhibit angiogenesis are disclosed in WO 91/19731. This document also discloses that the steroids are useful in treating glaucoma. There is, however, no suggestion to use the compounds for treating GLC1A glaucoma.

[0015] Alward et al., The New England Journal of Medicine (1998) 338, 1022-1027, Stone et al., Science (1997) 275, 668-670 and Alward et al., Journal of Glaucoma (1996) 5, 276-284 show that there are several forms of primary open angle glaucoma of which GLC1A glaucoma is only a subgroup.

Summary of the Invention

[0016] The invention is directed to the use of angiostatic agents for the manufacture of a medicament for controlling GLC1A glaucoma.

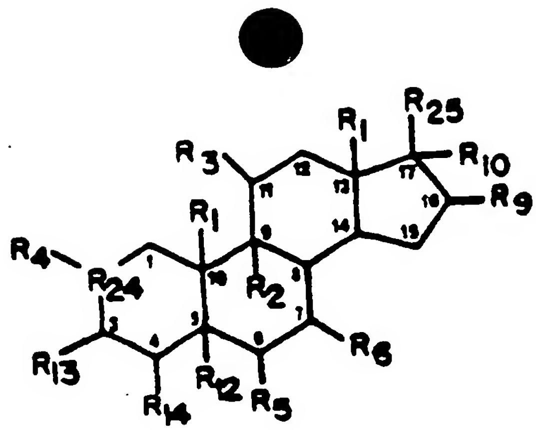
Detailed Description of Preferred Embodiments

[0017] Agents which alter the expression of GLC1A in the glaucomatous eye are expected to lower IOP and thereby prevent or inhibit the glaucomatous optic neuropathy which is being driven by elevated IOP. Glucocorticoids upregulte GLC1A expression in the TM of certain individuals. There have been several reports of elevated levels of the natural glucocorticid cortisol in the aqueous humor and plasma of glaucoma patients (Schwartz, et al., *supra;* Rozsival, et al., *supra).* In addition, certain mutations in GLC1A may alter the expression of GLC1A in the TM tissue of 1q glaucoma patients. Unexpectedly, it has been discovered that angiostatic agents inhibit the expression of GLC1A in cultured human TM cells and lower elevated IOP in certain animal models of ocular hypertension. The compounds thereby prevent the expression of GLC1A and the subsequent development of ocular hypertension.

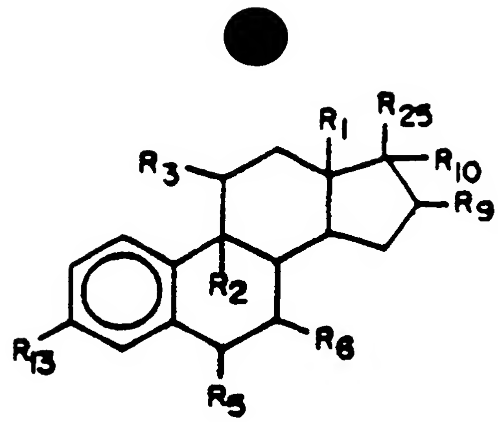
[0018] The development of blood vessels for the purpose of sustaining viable tissue is known as angiogenesis. Agents which inhibit angiogenesis are known by a variety of terms such as angiostatic, angiolytic or angiotropic agents. For purposes of this specification, the term "angiostatic agent" means compounds which can be used to inhibit angiogenesis.

[0019] The specific angiostatic agents of the present invention are steroids or steroid metabolites. For purposes herein, the term "angiostatic steroids" means steroids and steroid metabolites which inhibit angiogenesis. The present invention is based on the finding that angiostatic steroids can be used for the control of ocular hypertension. In particular, the agents can be used for the treatment of GLC1A glaucoma.

[0020] Preferred angiostatic steroids of the present invention have the following formula:



Structure [A]



Structure [B]

wherein

R_1 is H, β-CH_3 or β-C_2H_5;
R_2 is F, C_9-C_{11} double bond, C_9-C_{11} epoxy, H or Cl;
R_3 is H, OR_{26}, $OC(=O)R_{27}$, halogen, C_9-C_{11} double bond, C_9-C_{11} epoxy, =O, -OH, -O-alkyl(C_1-C_{12}), -OC(=O)alkyl (C_1-C_{12}), -OC(=O)ARYL, -OC(=O)N(R)$_2$ or -OC(=O)OR_7, wherein ARYL is furyl, thienyl, pyrrolyl, or pyridyl and each of said moieties is optionally substituted with one or two (C_1-C_4)alkyl groups, or ARYL is -$(CH_2)_f$-phenyl wherein f is 0 to 2 and the phenyl ring is optionally substituted with 1 to 3 groups selected from chlorine, fluorine, bromine, alkyl(C_1-C_3), alkoxy(C_1-C_3), thioalkoxy-(C_1-C_3), Cl_3C-, F_3C-, -NH_2 and -$NHCOCH_3$ and R is hydrogen, alkyl (C_1-C_4), or phenyl and each R can be the same or different, and R_7 is ARYL as herein defined, or alkyl(C_1-C_{12});
R_4 is H, CH_3, Cl or F;
R_5 is H, OH, F, Cl, Br, CH_3, phenyl, vinyl or allyl;
R_6 is H or CH_3;
R_9 is $CH_2CH_2OR_{26}$, $CH_2CH_2OC(=O)R_{27}$, H, OH, CH_3, F, =CH_2, $CH_2C(=O)OR_{28}$, OR_{26}, $O(C=O)R_{27}$ or $O(C=O)CH_2(C=O)OR_{26}$
R_{10} is -C≡CH, -CH=CH_2, halogen, CN, N_3, OR_{26}, $OC(=O)R_{27}$, H, OH, CH_3 or R_{10} forms a second bond between positions C-16 and C-17;
R_{12} is H or forms a double bond with R_1 or R_{14};
R_{13} is halogen, OR_{26}, $OC(=O)R_{27}$, NH_2, NHR_{26}, $NHC(=O)R_{27}$, $N(R_{26})_2$, $NC(=O)R_{27}$, N_3, H, -OH, =O, -O-P(=O)(OH)$_2$, or -O-C(=O)-$(CH_2)_t$COOH where t is an integer from 2 to 6;
R_{14} is H or forms a double bond with R_{12};
R_{15} is H, =O or -OH;
and R_{23} with R_{10} forms a cyclic phosphate;
wherein R_9 and R_{15} have the meaning defined above;
or wherein R_{23} is -OH, O-C(=O)-R_{11}, -OP(O)-(OH)$_2$, or -O-C(=O)-$(CH_2)_t$COOH wherein t is an integer from 2 to 6;
and R_{11} is -Y-$(CH_2)_n$-X-$(CH_2)_m$-SO_3H,
-Y'-$(CH_2)_p$-X'-$(CH_2)_q$-$NR_{16}R_{17}$ or -Z$(CH_2)_r$Q,
wherein Y is a bond or -O-; Y' is a bond, -O-, or -S-; each of X and X' is a bond,-CON(R_{18})-, -N(R_{18})CO-, -O-, -S-, -S(O)-, or -S(O_2)-; R_{18} is hydrogen or alkyl (C_1-C_4); each of R_{16} and R_{17} is a lower alkyl group of from 1 to 4 carbon atoms optionally substituted with one hydroxyl or R_{16} and R_{17} taken together with the nitrogen atom to which each is attached forms a monocyclic heterocycle selected from pyrrolidino, piperidino, morpholino, thiomorpholino, piperazino or N(lower)alkyl-piperazino wherein alkyl has from 1 to 4 carbon atoms; n is an integer of from 4 to 9; m is an integer of from 1 to 5; p is an integer of from 2 to 9; q is an integer of from 1 to 5;
Z is a bond or -O-; r is an integer of from 2 to 9; and Q is one of the following:

(1) -R_{19}-CH_2COOH wherein R_{19} is -S-, -S(O)-, -S(O)$_2$-, -$SO_2N(R_{20})$-, or $N(R_{20})SO_2$-; and R_{20} is hydrogen or

lower alkyl-(C_1-C_4); w[illegible]e proviso that the total number of carbon ato[illegible]R_{20} and $(CH_2)_r$ is not greater than 10; or

(2) -CO-COOH; or

(3) $CON(R_{21})CH(R_{22})COOH$ wherein R_{21} is H and R_{22} is H, CH_3, $-CH_2COOH$, $-CH_2CH_2COOH$, $-CH_2OH$, $-CH_2SH$, $-CH_2CH_2SCH_3$, or

$-CH_2Ph-OH$ wherein Ph-OH is p-hydroxyphenyl;

or R_{21} is CH_3 and R_{22} is H;

or R_{21} and R_{22} taken together are $-CH_2CH_2CH_2-$;

or $-N(R_{21})CH(R_{22})COOH$ taken together is $-NHCH_2CONHCH_2COOH$; and pharmaceutically acceptable salts thereof;

with the proviso that if R_{23} is a phosphate, it must form a cyclic phosphate, with R_{10} when R_{13} is = O, except for the compound wherein R_1 is β-CH_3, R_2 and R_3 taken together form a double bond between positions 9 and 11, R_4 and R_6 are hydrogen, R_{12} and R_{14} taken together form a double bond between positions 4 and 5, R_5 is $\propto$-F, R_9 is β-CH_3, R_{10} is $\propto$-OH, R_{13} and R_{15} are =O and

R_{23} is $-OP(O)-(OH)_2$.

R_{24} = C, C_1-C_2 double bond, O;

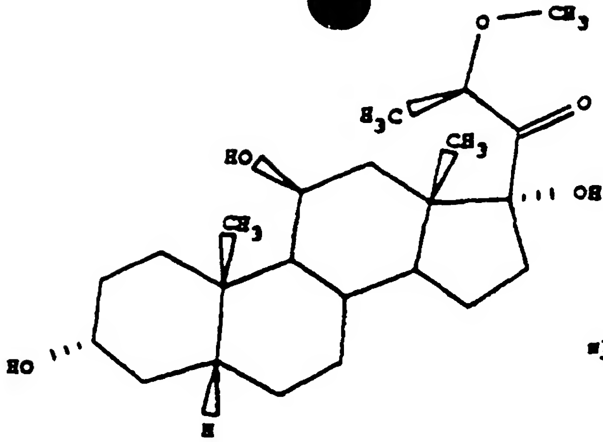
R_{25} = $C(R_{15})CH_2-R_{23}$, OH, OR_{26}, $OC(=O)R_{27}$, R_{26}, COOH, $C(=O)OR_{26}$, $CHOHCH_2OH$, $CHOHCH_2OR_{26}$, $CHOHCH_2OC(=O)R_{27}$, CH_2CH_2OH, $CH_2CH_2OR_{26}$, $CH_2CH_2OC(=O)R_{27}$, CH_2CN, CH_2N_3, CH_2NH_2, CH_2NHR_{26}, $CH_2N(R_{26})_2$, CH_2OH, CH_2OR_{26}, $CH_2O(C=O)R_{27}$, $CH_2O(P=O)(OH)_2$, $CH_2O(P=O)\ (OR_{26})_2$, CH_2SH, CH_2S-R_{26}, $CH_2SC(=O)R_{27}$, $CH_2NC(=O)R_{27}$, $C(=O)CHR_{28}OH$, $C(=O)CHR_{28}OR_{26}$, $C(=O)CHR_{28}OC(=O)R_{27}$ or R_{10} and R_{25} taken together may be $=C(R_{28})_2$, that is, an optionally alkyl substituted methylene group;

wherein R_{26} = C_1-C_6 (alkyl, branched alkyl, cycloalkyl, haloalkyl, aralkyl, aryl);

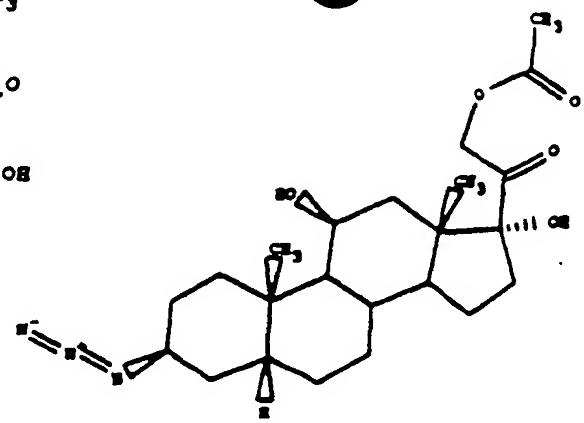
R_{27} = R_{26} + OR_{26}; R_{28} = H, C_1-C_6 (alkyl, branched alkyl, cycloalkyl).

[0021] Unless specified otherwise, all substituent groups attached to the cyclopentanophenanthrene moiety of Structures [A] and [B] may be in either the alpha or beta position. Additionally, the above structures include all pharmaceutically acceptable salts of the angiostatic steroids.

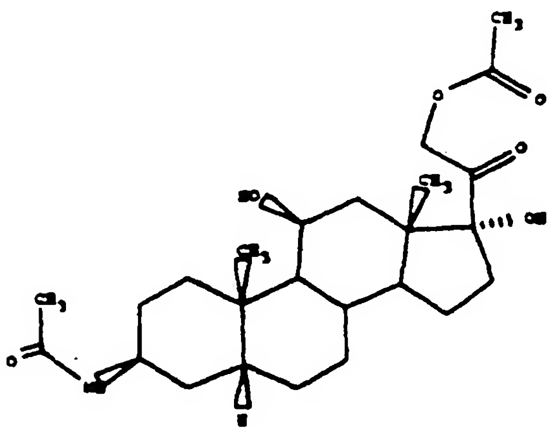
[0022] Preferred angiostatic steroids are:



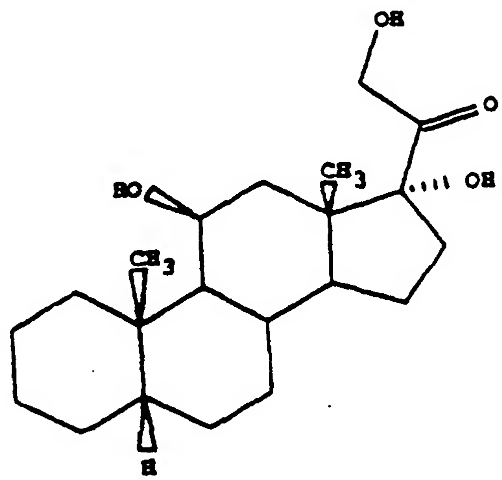
21-METHYL-5β-PREGNAN-3α,11β,17α,21-TETROL-20-ONE 21-METHYL ETHER



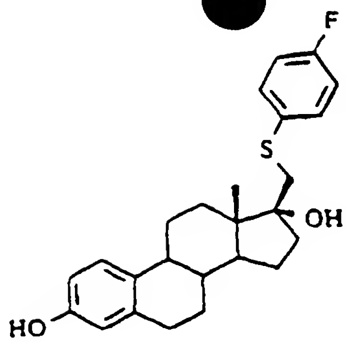
3β-AZIDO-5β-PREGNAN-11β,17α,21-TRIOL-20-ONE-21-ACETATE



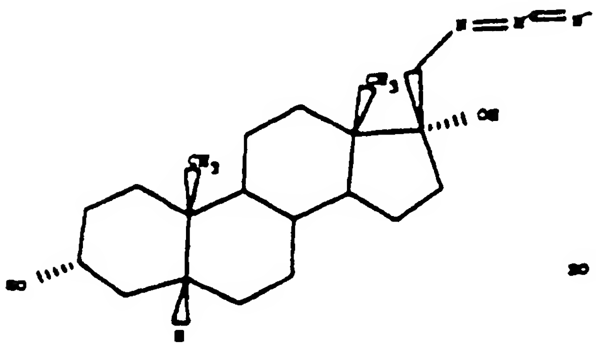
3β-ACETAMIDO-5β-PREGNAN-11β,17α,21-TRIOL-20-ONE 21-ACETATE



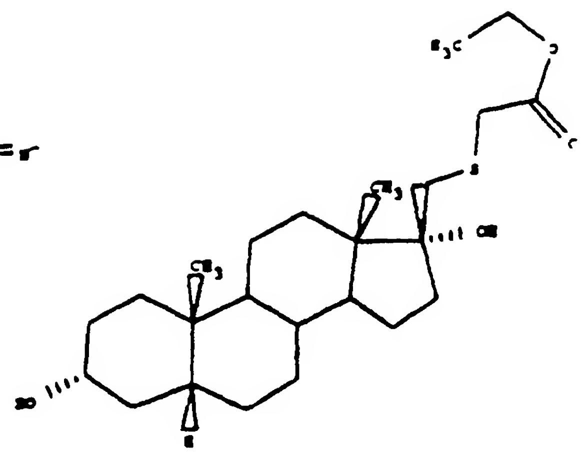
5β-PREGNAN-11β,17α,21-TRIOL-20-ONE



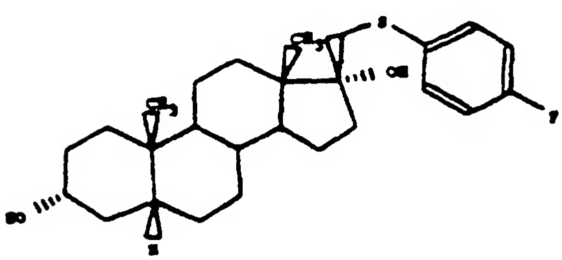
17-((4-FLUORO)THIOPHENOXY)METHYL-1,3,5-ESTRATRIEN-3,17-DIOL



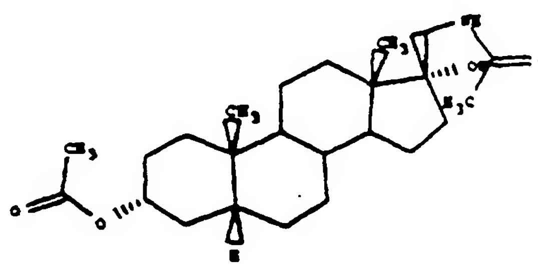
20-AZIDO-21-NOR-5β-PREGNAN-3α, 17α-DIOL



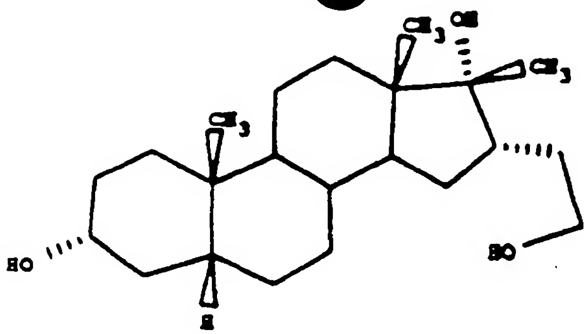
20-(CARBETHOXYMETHYL)THIO-21-NOR-5β-PREGNAN-3α, 17α-DIOL



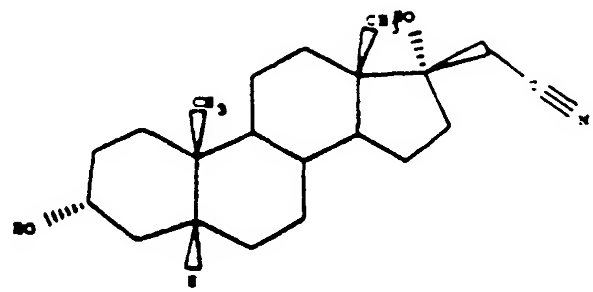
20-(4-FLUOROPHENYL)THIO-21-NOR-PREGNAN-3α,17α-DIOL



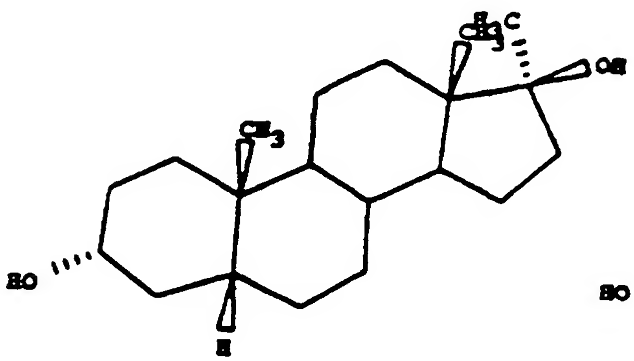
20-ACETAMIDO-21-NOR-5β–PREGNAN-3α–5β–17α-DIOL-3-ACETATE



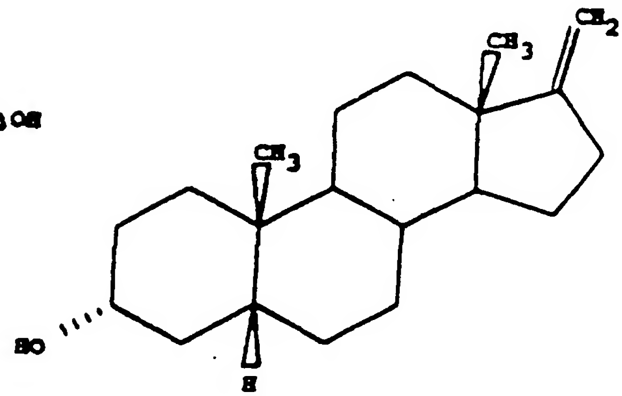
16α-(2-HYDROXYETHYL)-17β-METHYL-5β-ANDROSTAN-3α,17α-DIOL



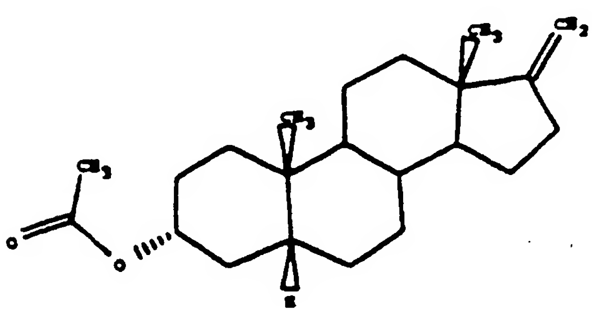
20-CYANO-21-NOR--5β-PREGNAN-3α,17α-DIOL



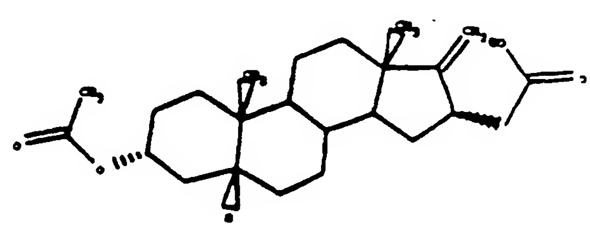
17α-METHYL-5β-ANDROSTAN-3α,17β-DIOL



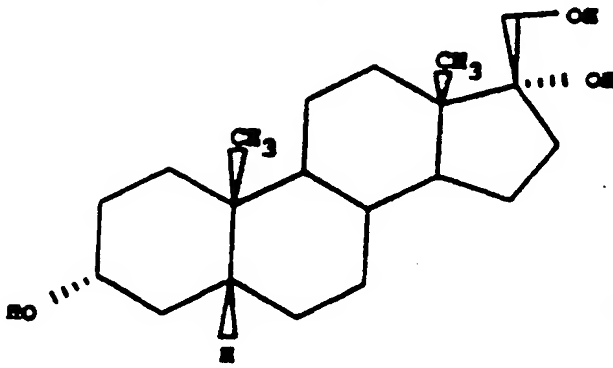
21-NOR-5β-PREGN-17(20)-EN-3α-OL



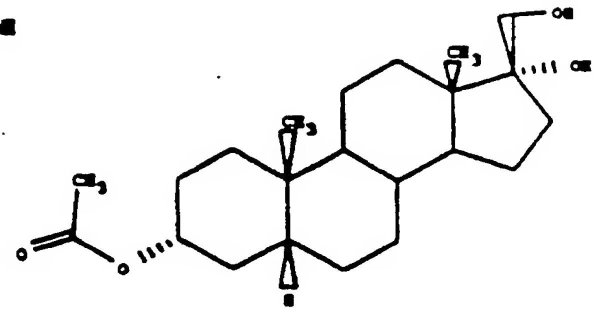
21-NOR-5β-PREGN-17(20)-EN-3α-OL-3-ACETATE



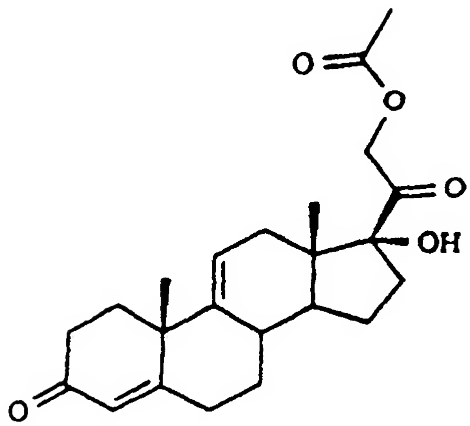
21-NOR-5β-PREGN-17(20)-EN-3α-OL-16-ACETIC ACID-3-ACETATE



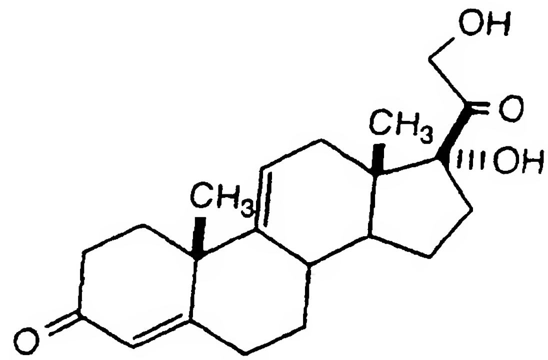
21-NOR-5β-PREGNAN-3α,17α,20-TRIOL



21-NOR-5β-PREGNAN-3α,17α,20-TRIOL-3-ACETATE



4,9(11)-PREGNADIEN-17∝,21-DIOL-3,20-DIONE-21-ACETATE



4,9(11)-PREGNADIEN-17∝,21-DIOL-3,20-DIONE

[0023] The more preferred compounds are 21-methyl-5β-pregnan-3∝, 11β, 17∝,21-tetrol 20-one-21-methyl ether; 3β-azido-21-acetoxy-5β-pregnan-11β, 17∝-diol-20-one; 3β-acetamido-21-acetoxy-5β-pregnan-11β, 17∝-diol-20-one; and 5β-pregnan-11β,17∝, 21-triol-20-one. The most preferred compounds are 4,9(11)-pregnadien-17∝,21-diol-3,20-dione-21-acetate and 4,9(11)-pregnadien-17∝,21-diol-3,20-dione.

[0024] The angiostatic steroids of the present invention may be incorporated in various formulations for delivery to the eye. For example, topical formulations can be used and can include ophthalmologically acceptable preservatives, surfactants, viscosity enhancers, buffers, sodium chloride and water to form aqueous sterile ophthalmic solutions and suspensions. In order to prepare sterile ophthalmic ointment formulations, an angiostatic steroid is combined with a preservative in an appropriate vehicle, such as mineral oil, liquid lanolin or white petrolatum. Sterile ophthalmic gel formulations comprising the angiostatic steroids of the present invention can be prepared by suspending an angiostatic steroid in a hydrophilic base prepared from a combination of, for example, Carbopol-940 (a carboxyvinyl polymer

available from the B.F. Goodric[illegible]pany) according to published formulations for a[illegible]ous ophthalmic preparations. Preservatives and tonicity agents may also be incorporated in such gel formulations.

[0025] The specific type of formulations selected will depend on various factors, such as the angiostatic steroid or its salt being used, and the dosage frequency. Topical ophthalmic aqueous solutions, suspensions, ointments and gels are the preferred dosage forms. The angiostatic steroid will normally be contained in these formulations in an amount of from about 0.005 to about 5.0 weight percent (wt.%). Preferable concentrations range from about 0.05 to about 2.0 wt.%. Thus, for topical administration, these formulations are delivered to the surface of the eye one to four times per day, depending upon the routine discretion of the skilled clinician.

[0026] The following examples illustrate formulations and synthesis of compounds of the present invention, but are in no way limiting.

Example 1

[0027]

Component	wt.%
Angiostatic Steroid	0.005-5.0
Tyloxapol	0.01-0.05
HPMC	0.5
Benzalkonium Chloride	0.01
Sodium Chloride	0.8
Edetate Disodium	0.01
NaOH/HCl	q.s. pH 7.4
Purified Water	q.s. 100 mL

Example 2

[0028]

Component	wt.%
4,9(11)-pregnadien-17α,21-diol-3,20-dione-21-acetate	1.0
Mannitol	2.40
Carbopol 974P	0.50
Polysorbate 80	0.05
Benzalkonium Chloride	0.01
Sodium Chloride	0.4
Edetate Disodium	0.01
NaOH/HCl	q.s. pH 7.4
Purified Water	q.s. 100 mL

Example 3

Preparation of 5β-Pregnan-11β, 17α, 21-triol-20-one

Tetrahydrocortisol-F-21-t-butyldiphenylsilyl ether (PS03842)

[0029] A solution of 4.75 g (17.3 mmol) of t-butyldiphenylchlorosilane in 5 mL of dry DMF was added dropwise to a stirred solution of 5.7 g (15.6 mmol) of tetrahydrocortisol-F (Steraloids No. P9050) and 2.3 g (19 mmol) of 4-dimethylaminopyridine (DMAP) in 30 mL of dry DMF, under N_2, at -25 to -30°C (maintained with CO_2 - MeCN). After a further 20 min at -30°C, the mixture was allowed to warm to 23°C overnight.

[0030] The mixture was partitioned between ether and water, and the organic solution was washed with brine, dried ($MgSO_4$), filtered and concentrated to give 10.7 g of a white foam.

[0031] This material was purified by flash column chromatography (400 g silica; 62.5 to 70% ether/hexane). The 3-siloxy isomer eluted first, followed by mixed fractions, followed by the title compound. The concentrated mixed fractions (4.0 g) were chromatographed on the same column with 35% ethyl acetate/hexane. The total yield of the 3-siloxy

isomer was 0.42 g (5%), and of the title compound, 5.05 g (53.5%). Continued elution with 25% MeOH/EtOAc allowed recovery of unreacted tetrahydrocortisol-F.

PSO3842

[0032] NMR (200 MHz ^{1}H) ($CDCl_3$): δ0.63 (s, 3H, Me-18); 1.11 (s, 9H, t-Bu); 1.12 (s, 3H, Me-19); 2.57 (t, J=13, 1H, H-8); 2.6 (s, 1H, OH-17); 3.63 (sept, J=2.5, 1H, H-3); 4.15 (br s, 1H, H-11); 4.37 and 4.75 (AB, J=20, 2H, H-21); 7.4 (m, 6H) and 7.7 (m, 4H) (Ph_2).
NMR (200 MHz ^{1}H) (DMSO-d_6): δ0.64 (s, 3H, Me-18); 1.02 (s, 9H, t-Bu); 1.07 (s, 3H, Me-19); 2.50 (t, J=13, 1H, H-8); 3.37 (m, 1H, H-3); 3.94 (d, J=2, 1H, OH-11); 4.00 (br s, 1H, H-11); 4.42 (d, J=5, 1H, OH-3); 4.38 and 4.83 (AB, J=20, 2H, H-21); 5.11 (s, 1H, OH-17); 7.45 (m, 6H) and 7.6 (m, 4H) (Ph_2).
NMR (50.3 - MHz ^{13}C) ($CDCl_3$): 17.4 (C-18); 19.3 (C-16); 23.7 (C-15); 26.3 (C-7); 26.6 (C-19); 26.8 (Me_3C); 27.2 (C-6); 30.9 (C-2); 31.5 (C-8); 34.1 (Me_3C); 34.8 (C-10); 35.2 (C-1); 36.2 (C-4); 39.7 (C-13); 43.5 (C-5); 44.3 (C-9); 47.4 (C-12); 52.1 (C-14); 67.8 (C-11); 68.9 (C-21); 71.7 (C-3); 89.8 (C-14); 127.8, 129.8, 132.8, 132.9, 135.7, 135.8 (diastereotopic Ph_2); 208.8 (C-20). Underlined resonances showed inversion in the APT experiment. Assignments: E. Breitmaier, W. Voelter "Carbon-13 NMR Spectroscopy," 3d ed., VCH, 1987; pp. 345-348.
[0033] IR (KBr) 3460, 2930, 2860, 1720, 1428, 1136, 1113, 1070, 1039, 703 cm^{-1}.
[0034] This compound did not show a sharp melting point but turned to a foam at 80-100°C. Numerous attempts at recrystallization failed.

5β-Pregnan-11β, 17α, 21-triol-20-one

[0035] A solution of PSO3842 (0.91 g, 1.50 mmol) and thiocarbonyl diimidazoie (1.05 g, 5.9 mmol) in 8 mL of anhydrous dioxane was refluxed under N_2 for 3.5 h. The cooled solution was partitioned between ether and water and the organic solution was washed with brine, dried ($MgSO_4$), filtered and concentrated. The residue was chromatographed (120 g SiO_2, 35% EtOAc/hexane) giving 0.86 g (80%) of the imidazolyl thioester.
[0036] A solution of 0.75 g (1.05 mmol) of this compound in 100 mL of anhydrous dioxane was added dropwise over 2.2 h to a rapidly stirred, refluxing solution of 1.6 mL (5.9 mmol) of Bu_3SnH in 100 mL of anhydrous dioxane under N_2. After a further 1 h at reflux, the solution was cooled, concentrated and the residue chromatographed (200 g SiO_2, 9% EtOAc/hexane) giving 0.43 g (70%) of the 3-deoxy-21-silyl ether. This material was dissolved in 20 mL of methanol; $Bu_4NF \cdot 3H_2O$ (0.50 g, 1.6 mmol) was added, and the mixture was heated to reflux under N_2 for 4 h. The cooled solution was diluted with 2 volumes of EtOAc, concentrated to 1/4 volume, partitioned (EtOAc/H_2O), and the organic solution was washed with brine, dried ($MgSO_4$), filtered and concentrated. The residue (0.40 g) was chromatographed (30 g SiO_2, 40% EtOAc/hexane) to give 0.25 g (98%) of an oil.
[0037] This oil was crystallized (n-BuCl) to afford 0.14 g of the title compound as a white solid, m.p. 167-170°C.
[0038] IR (KBr): 3413 (br), 2934, 1714, 1455, 1389, 1095, 1035 cm^{-1}.
[0039] MS (Cl): 351 (M+1).
[0040] NMR (200 MHz ^{1}H, DMSO-d_6): δ0.69 (s, 3H, Me-18); 1.14 (s, 3H, Me-19); 0.8-2.0 (m); 2.5 (t, J=13, 1H, H-8); 3.96 (d, J=2, 1H, OH-11); 4.1 (br s, 1H, H-11); 4.1 and 4.5 (AB, further split by 5 Hz, 2H, H-21); 4.6 (t, J=5,1H, OH-21); 5.14 (s, 1H, OH-17).
[0041] Anal. Calc'd for $C_{21}H_{34}O_4$: C, 71.96; H, 9.78.
Found: C, 71.69; H, 9.66.

Example 4

Preparation of 21-Methyl-5β-pregnan-3α, 11β, 17α, 21-tetrol-20-one 21-methyl ether

[0042] Sodium hydride (60% oil dispersion, 0.10 g, 2.5 mmol) was added to a stirred solution of tetrahydrocortisol-F (0.73 g, 2.0 mmol) and CH_3I (0.60 mL, 9.6 mmol) in 8 mL of anhydrous DMF under N_2. Hydrogen was evolved, and the temperature rose to 35°C. After 1 h, the mixture was diluted with EtOAc, extracted with water (until neutral) and brine, dried ($MgSO_4$), filtered and concentrated. The residue was chromatographed (70 g SiO_2, 80% EtOAc/hexane) to give 0.17 g of a white solid, MS (Cl) = 395 (M +1). This material was recrystallized (EtOAc-n-BuCl) to afford 0.12 g (16%) of the title compound as a feathery white solid, m.p. 208-213 °C.
[0043] IR (KBr): 3530, 3452, 2939, 2868, 1696 (s, CO), 1456, 1366, 1049 cm^{-1}.
[0044] NMR (200 MHz ^{1}H, DMSO-d_6): δ0.74 (s, 3H, Me-18); 1.09 (s, 3H, Me-19); 1.14 (d, J=6.6, 3H, C-21 Me); 0.8-2.0 (m); 2.47 (t, J=13, 1H, H-8); 3.18 (s, 3H, OMe); 3.35 (m, 1H, H-3); 4.00 (d, J=2, 1H, OH-11); 4.07 (brs, 1H, H-11); 4.37 (q, J=6.6, 1H, H-21); 4.43 (d, J=5, 1H, OH-3); 5.16 (s, 1H, OH-17).
[0045] Anal. Calc'd for $C_{23}H_{38}O_5$: C, 70.01; H, 9.71.

Found: C, 70.06; H[illegible].

Example 5

Preparation of 3β-Azido-21-acetoxy-5β-pregnan-11β, 17∝-diol-20-one

[0046] A solution of triphenylphosphine (2.6 g, 10 mmol) in 10 mL of toluene was carefully added to a stirred solution of PS03842 (see Example 4) (1.75 g, 2.90 mmol), diphenylphosphoryl azide (2.2 mL, 10.2 mmol) and diethyl azodicarboxylate (1.55 mL, 10 mmol) under N_2, keeping the internal temperature below 35°C (exothermic). The solution was stirred for 1.2 h, then diluted with ether, washed with water and brine, dried ($MgSO_4$), filtered and concentrated and the residue (9.5 g, oil) chromatographed 175 g SiO_2, 15% EtOAc/hexane) giving 1.83 g of a viscous oil.

[0047] A solution of 1.73 g of this material and 1.75 g (5.5 mmol) of $Bu_4NF{\cdot}3H_2O$ in 20 mL of methanol was refluxed under N_2 for 2.5 h. The crude product (1.94 g) was isolated with ethyl acetate and chromatographed (100 g SiO_2, 50% EtOAc/hexane) giving 0.60 g (56%) of a white semisolid. Trituration (4:1 hexane-ether) gave 0.57 g (53%) of a solid.

[0048] A stirred solution of 0.40 g of this material in 3 mL of dry pyridine was treated with 0.3 mL of acetic anhydride and stirred overnight at 23°C under N_2. The mixture was quenched with 1 mL of methanol, stirred for 15 min, diluted with ether, washed with 1 M aqueous HCl, water (until neutral), brine, dried (MgSO4), filtered and concentrated. The residue (0.41 g, oil) was chromatographed (35 g SiO_2, 33% EtOAc/hexane) to afford 0.33 g (76%) of the title compound as a white foam, m.p. 80-90°C (dec).

[0049] IR (KBr): 3505, 2927, 2866, 2103 (vs), 1721 (sh 1730), 1268, 1235 cm^{-1}.

[0050] NMR (200 MHz ^1H, $CDCl_3$): δ0.92 (s, 3H, Me-18); 1.21 (s, 3H, Me-19); 1.0-2.1 (m); 2.17 (s, 3H, Ac); 2.25 (s 1H, OH-17); 2.74 (m, 1H, H-8); 3.97 (br s, 1H, H-3); 4.31 (br s, 1H, H-11); 4.94 (AB, J=17, Δv=60, 2H, H-21).

[0051] Anal. Calc'd for $C_{23}H_{35}N_3O_5$: C, 63.72; H, 8.14; N, 9.69.
Found: C, 63.39; H, 8.18; N, 9.45.

Example 6

Preparation of 3β-Acetamido-21-acetoxy-5β-pregnan-11β, 17∝-diol-20-one

[0052] A solution of 3β-azido-21-acetoxy-5β-pregnan-11β,17∝-diol-20-one (0.15 g, 0.35 mmol) in 8 mL of absolute ethanol containing 0.03 g of 10% Pd on C was stirred under H_2 (1 atm) at 23°C for 2 h. The mixture was filtered and concentrated, the residue dissolved in EtOAc, the basic material extracted into 1 M aqueous HCl, liberated (Na_2CO_3), extracted (EtOAc) and the organic extract washed with water (until neutral) and brine, dried ($MgSO_4$), filtered and concentrated to provide 58 mg of a solid.

[0053] This material was acetylated (1.0 mL of dry pyridine, 0.20 mL of Ac_2O, 23°C, N_2, overnight), followed by workup (as described for the steroid of Example 6 [last step]) affording a crude product that was chromatographed (25 g SiO_2, EtOAc). This product was triturated with ether to afford 51 mg (33%) of product as a white solid, m.p. 179-181°C.

[0054] Ms (Cl, isobutane): (M +1) = 450 (M^+), 432, 391, 371, 348.

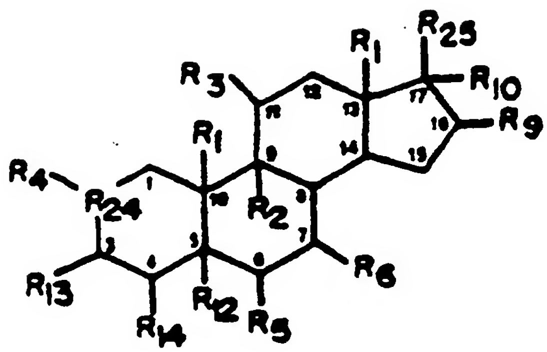
[0055] IR (KBr): 3398 (br), 2932, 2865, 1720 (sh. 1740), 1652, 1538, 1375, 1265, 1236 cm^{-1}.

[0056] NMR (200 MHz ^1H, $CDCl_3$): δ0.89, 1.22, 1.99, 2.17 (all s, 3H); 1.0-2.2(m); 2.7 (t, J=13, 1H, H-8); 3.03 (s, 1H, OH-17); 4.2 (br s, 1H, H-11); 4.3 (br s, 1H, H-3); 4.96 (AB, J=17.5, Δv=42, 2H, H-21); 5.8 (d, J=10, 1H, NH).

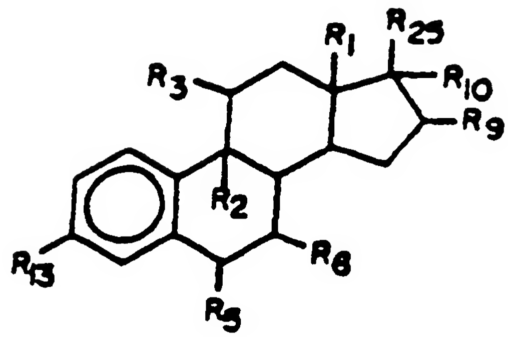
Claims

1. Use of an angiostatic agent for the manufacture of a medicament for treating GLC1A glaucoma.

2. Use of Claim 1 wherein the angiostatic agent has the following structure:



Structure [A]



Structure [B]

wherein

R_1 is H, β-CH_3 or β-C_2H_5;
R_2 is F, C_9-C_{11} double bond, C_9-C_{11} epoxy, H or Cl;
R_3 is H, OR_{26}, $OC(=O)R_{27}$, halogen, C_9-C_{11} double bond, C_9-C_{11} epoxy, =O, -OH, -O-alkyl(C_1-C_{12}), -OC(=O)alkyl(C_1-C_{12}), -OC(=O)ARYL, -OC(=O)N(R)$_2$ or
-OC(=O)OR_7, wherein ARYL is furyl, thienyl, pyrrolyl, or pyridyl and each of said moieties is optionally substituted with one or two (C_1-C_4)alkyl groups, or ARYL is -$(CH_2)_f$-phenyl wherein f is 0 to 2 and the phenyl ring is optionally substituted with 1 to 3 groups selected from chlorine, fluorine, bromine, alkyl(C_1-C_3), alkoxy(C_1-C_3), thioalkoxy-(C_1-C_3), Cl_3C-, F_3C-, -NH_2 and -$NHCOCH_3$ and R is hydrogen, alkyl (C_1-C_4), or phenyl and each R can be the same or different, and R_7 is ARYL as herein defined, or alkyl(C_1-C_{12});
R_4 is H, CH_3, Cl or F;
R_5 is H, OH, F, Cl, Br, CH_3, phenyl, vinyl or allyl;
R_6 is H or CH_3;
R_9 is $CH_2CH_2OR_{26}$, $CH_2CH_2OC(=O)R_{27}$, H, OH, CH_3, F, =CH_2, $CH_2C(=O)OR_{28}$., OR_{26}, $O(C=O)R_{27}$ or O(C=O)CH_2(C=O)OR_{26}
R_{10} is -C≡CH, -CH=CH_2, halogen, CN, N_3, OR_{26}, $OC(=O)R_{27}$, H, OH, CH_3 or R_{10} forms a second bond between positions C-16 and C-17;
R_{12} is H or forms a double bond with R_1 or R_{14};
R_{13} is halogen, OR_{26}, $OC(=O)R_{27}$, NH_2, NHR_{26}, $NHC(=O)R_{27}$, $N(R_{26})_2$, $NC(=O)R_{27}$, N_3, H, -OH, =O, -O-P(=O)(OH)$_2$, or -O-C(=O)-$(CH_2)_t$COOH where t is an integer from 2 to 6;
R_{14} is H or forms a double bond with R_{12};
R_{15} is H, =O or -OH;
and R_{23} with R_{10} forms a cyclic phosphate;
wherein R_9 and R_{15} have the meaning defined above;
or wherein R_{23} is -OH, O-C(=O)-R_{11}, -OP(O)-(OH)$_2$, or -O-C(=O)-$(CH_2)_t$COOH wherein t is an integer from 2 to 6; and R_{11} is -Y-$(CH_2)_n$-X-$(CH_2)_m$-SO_3H, -Y'-$(CH_2)_p$-X'-$(CH_2)_q$-$NR_{16}R_{17}$ or -Z$(CH_2)_r$Q,
wherein Y is a bond or -O-; Y' is a bond, -O-, or -S-; each of X and X' is a bond,-CON(R_{18})-, -N(R_{18})CO-, -O-, -S-, -S(O)-, or -S(O_2)-; R_{18} is hydrogen or alkyl (C_1-C_4); each of R_{16} and R_{17} is a lower alkyl group of from 1 to 4 carbon atoms optionally substituted with one hydroxyl or R_{16} and R_{17} taken together with the nitrogen atom to which each is attached forms a monocyclic heterocycle selected from pyrrolidino, piperidino, morpholino, thiomorpholino, piperazino or N(lower)alkyl-piperazino wherein alkyl has from 1 to 4 carbon atoms; n is an integer of from 4 to 9; m is an integer of from 1 to 5; p is an integer of from 2 to 9; q is an integer of from 1 to 5;
Z is a bond or -O-; r is an integer of from 2 to 9; and Q is one of the following:

(1) -R_{19}-CH_2COOH wherein R_{19} is -S-, -S(O)-, -S(O)$_2$-, -$SO_2N(R_{20})$-, or $N(R_{20})SO_2$-; and R_{20} is hydrogen

or lower alkyl-(C_1 [illegible] with the proviso that the total number of carb[illegible]oms in R_{20} and $(CH_2)_r$ is not greater than 10; or
(2) -CO-COOH; or
(3) $CON(R_{21})CH(R_{22})COOH$ wherein R_{21} is H and R_{22} is H, CH_3, $-CH_2COOH$, $-CH_2CH_2COOH$, $-CH_2OH$, $-CH_2SH$, $-CH_2CH_2SCH_3$, or
$-CH_2Ph-OH$ wherein Ph-OH is p-hydroxyphenyl;
or R_{21} is CH_3 and R_{22} is H;
or R_{21} and R_{22} taken together are $-CH_2CH_2CH_2-$;
or $-N(R_{21})CH(R_{22})COOH$ taken together is $-NHCH_2CONHCH_2COOH$; and pharmaceutically acceptable salts thereof;
with the proviso that if R_{23} is a phosphate, it must form a cyclic phosphate, with R_{10} when R_{13} is = O, except for the compound wherein R_1 is β-CH_3, R_2 and R_3 taken together form a double bond between positions 9 and 11, R_4 and R_6 are hydrogen, R_{12} and R_{14} taken together form a double bond between positions 4 and 5, R_5 is ∝-F, R_9 is β-CH_3, R_{10} is ∝-OH, R_{13} and R_{15} are =O and
R_{23} is $-OP(O)-(OH)_2$.

R_{24} = C, C_1-C_2 double bond, O;
R_{25} = $C(R_{15})CH_2-R_{23}$, OH, OR_{26}, $OC(=O)R_{27}$, R_{26}, COOH, $C(=O)OR_{26}$, $CHOHCH_2OH$, $CHOHCH_2OR_{26}$, $CHOHCH_2OC(=O)R_{27}$, CH_2CH_2OH, $CH_2CH_2OR_{26}$, $CH_2CH_2OC(=O)R_{27}$, CH_2CN, CH_2N_3, CH_2NH_2, CH_2NHR_{26}, $CH_2N(R_{26})_2$, CH_2OH, CH_2OR_{26}, $CH_2O(C=O)R_{27}$, $CH_2O(P=O)(OH)_2$, $CH_2O(P=O)(OR_{26})_2$, CH_2SH, CH_2S-R_{26}, $CH_2SC(=O)R_{27}$, $CH_2NC(=O)R_{27}$, $C(=O)CHR_{28}OH$, $C(=O)CHR_{28}OR_{26}$, $C(=O)CHR_{28}OC(=O)R_{27}$ or R_{10} and R_{25} taken together may be $=C(R_{28})_2$, that is, an optionally alkyl substituted methylene group;

wherein R_{26} = C_1-C_6 (alkyl, branched alkyl, cycloalkyl, haloalkyl, aralkyl, aryl);
R_{27} = R_{26} + OR_{26}; R_{28} = H, C_1-C_6 (alkyl, branched alkyl, cycloalkyl).

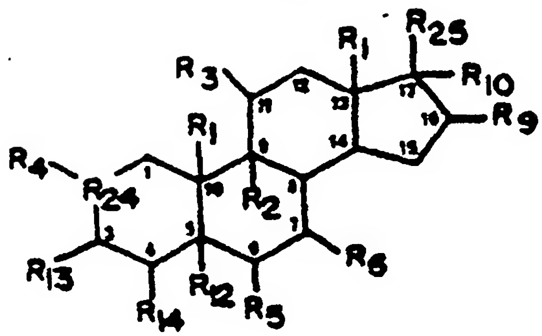
3. Use of Claim 2 wherein the compound is selected from the group consisting of 21-methyl-5β-pregnan-3∝,11β, 17∝, 21-tetrol-20-one 21-methyl ether; 3β-azido-21-acetoxy-5β-pregnan-11β, 17∝-diol-20-one; 3β-acetamido-21-acetoxy-5β-pregnan-11β, 17∝-diol-20-one; 5β-pregnan-11β, 17∝, 21-triol-20-one; 4, 9(11)-pregnadien-17∝, 21-diol-3,20-dione-21-acetate and 4,9(11)-pregnadien-17∝,21-diol-3,20-dione.

4. Use of Claim 3 wherein the compound is selected from the group consisting of 4, 9(11)-pregnadien-17∝,21-diol-3,20-dione-21-acetate and 4, 9(11)-pregnadien-17∝,21-diol-3,20-dione.

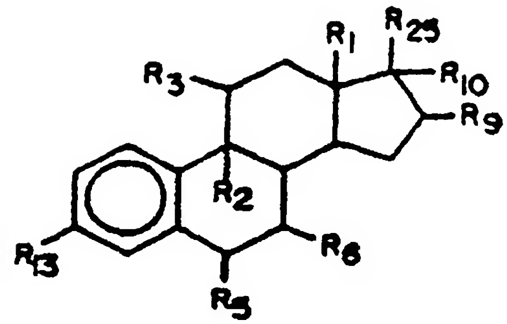
Patentansprüche

1. Verwendung eines angiostatischen Mittels zur Herstellung eines Arzneimittels zur Behandlung von GLC1A-Glaukom.

2. Verwendung nach Anspruch 1, wobei das angiostatische Mittel die folgende Strukturformel hat:



Strukturformel (A)



Strukturformel (B)

worin

R_1 H, β-CH_3 oder β-C_2H_5 ist;
R_2 F, eine C_9-C_{11}-Doppelbindung, eine C_9-C_{11}-Epoxygruppe, H oder Cl ist;
R_3 H, OR_{26}, $OC(=O)R_{27}$, Halogen, eine C_9-C_{11}-Doppelbindung, C_9-C_{11}-Epoxygruppe, =O, -OH, -O-Alkyl (C_1-C_{12}), -OC(=O)-Alkyl(C_1-C_{12}), -OC(=O)ARYL, $-OC(=O)N(R)_2$ oder $-OC(=O)OR_7$ ist, wobei ARYL ein Furyl-, Thienyl-, Pyrrolyl- oder Pyridylrest ist und jeder dieser Reste gegebenenfalls mit einer oder zwei (C_1-C_4)-Alkylgruppen substituiert ist oder ARYL ein -$(CH_2)_f$-Phenylrest ist, wobei f 0 bis 2 ist und der Phenylring gegebenenfalls mit 1 bis 3 Gruppen substituiert ist, die ausgewählt sind aus Chlor, Fluor, Brom, Alkyl(C_1-C_3), Alkoxy(C_1-C_3), Thioalkoxy(C_1-C_3), Cl_3C-, F_3C-, $-NH_2$ und $-NHCOCH_3$ und R Wasserstoff, Alkyl(C_1-C_4) oder Phenyl ist und jeder der Reste R gleich oder verschieden sein kann und R_7 ARYL, wie oben definiert ist, oder Alkyl(C_1-C_{12}) ist;
R_4 H, CH_3, Cl oder F ist;
R_5 H, OH, F, Cl, Br, CH_3, Phenyl, Vinyl oder Allyl ist;
R_6 H oder CH_3 ist;
R_9 $CH_2CH_2OR_{26}$, $CH_2CH_2OC(=O)R_{27}$, H, OH, CH_3, F, $=CH_2$, $CH_2C(=O)OR_{28}$, OR_{26}, $O(C=O)R_{27}$ oder $O(C=O)CH_2(C=O)OR_{26}$ ist;
R_{10} -C≡CH, $-CH=CH_2$, Halogen, CN, N_3, OR_{26}, $OC(=O)R_{27}$, H, OH, CH_3 ist oder R_{10} eine zweite Bindung an den Positionen C16 und C17 bildet;
R_{12} H ist oder eine Doppelbindung mit R_1 oder R_{14} bildet;
R_{13} Halogen, OR_{26}, $OC(=O)R_{27}$, NH_2, NHR_{26}, $NHC(=O)R_{27}$, $N(R_{26})_2$, $NC(=O)R_{27}$, N_3, H, -OH, =O, $-O-P(=O)(OH)_2$ oder $-O-C(=O)-(CH_2)_tCOOH$ ist, worin t eine ganze Zahl von 2 bis 6 ist;
R_{14} H ist oder eine Doppelbindung mit R_{12} bildet;
R_{15} H, =O oder -OH ist; und
R_{23} mit R_{10} ein cyclisches Phosphat bildet,
wobei R_9 und R_{15} die oben definierte Bedeutung haben;
oder wobei R_{23} -OH, $O-C(=O)R_{11}$, $-OP(O)-(OH)_2$ oder $-O-C(=O)-(CH_2)_tCOOH$ ist, worin t eine ganze Zahl von 2 bis 6 ist und R_{11} $-Y-(CH_2)_n-X-(CH_2)_m-SO_3H$, $-Y'-(CH_2)_p-X'-(CH_2)_q-NR_{16}R_{17}$ oder $-Z(CH_2)_rQ$ ist, wobei Y eine Bindung oder -O- ist; Y' eine Bindung, -O- oder -S- ist; X und X' jeweils eine Bindung, $-CON(R_{18})-$, $-N(R_{18})CO-$, -O-, -S-, -S(O)- oder $-S(O_2)-$ sind; R_{18} Wasserstoff oder Alkyl(C_1-C_4) ist; jeder der Reste R_{16} und R_{17} eine Niedrigalkylgruppe mit 1 bis 4 Kohlenstoffatomen ist, die gegebenenfalls mit einem Hydroxylrest substituiert ist oder R_{16} und R_{17} zusammen mit dem Stickstoffatom, an das sie jeweils gebunden sind, einen monocyclischen Heterocyclus bilden ausgewählt aus Pyrrolidino, Piperidino, Morpholino, Thiomorpholino, Piperazino oder N-(Niedrig)alkylpiperazino, wobei der Alkylrest 1 bis 4 Kohlenstoffatome hat; n eine ganze Zahl von 4 bis 9 ist; m eine ganze Zahl von 1 bis 5 ist; p eine ganze Zahl von 2 bis 9 ist; q eine ganze Zahl von 1 bis 5 ist; Z eine Bindung oder -O- ist; r eine ganze Zahl von 2 bis 9 ist und Q eine der folgenden Bedeutungen hat:

(1) $-R_{19}-CH_2COOH$, worin R_{19} -S-, -S(O)-, $-S(O)_2-$, $-SO_2N(R_{20})-$ oder $N(R_{20})SO_2-$ ist und R_{20} Wasserstoff oder ein Niedrigalkyl-(C_1-C_4)-Rest ist, mit dem Vorbehalt, dass die Gesamtanzahl an Kohlenstoffatomen in R_{20} und $(CH_2)_r$ nicht größer als 10 ist oder
(2) -CO-COOH oder
(3) $CON(R_{21})CH(R_{22})COOH$ ist, worin R_{21} H ist und R_{22} H, CH_3, $-CH_2COOH$, $-CH_2CH_2COOH$, $-CH_2OH$, $-CH_2SH$, $-CH_2CH_2SCH_3$ oder
$-CH_2Ph-OH$ ist, worin Ph-OH ein p-Hydroxyphenylrest ist oder
R_{21} CH_3 ist und R_{22} H ist;
oder R_{21} und R_{22} zusammen $-CH_2CH_2CH_2-$ sind;
oder $-N(R_{21})CH(R_{22})COOH$ zusammengenommen $-NHCH_2CONHCH_2COOH$ ist, und pharmazeutisch annehmbare Salze davon, mit dem Vorbehalt, dass R_{23} dann, wenn es ein Phosphat ist, ein cyclisches Phosphat bilden muss mit R_{10}, wenn R_{13} =O ist, außer für die Verbindung, worin R_1 β-CH_3 ist, R_2 und R_3 zusammen eine Doppelbindung zwischen den Positionen 9 und 11 bilden, R_4 und R_6 Wasserstoff sind, R_{12} und R_{14} zusammen eine Doppelbindung zwischen den Positionen 4 und 5 bilden, R_5 α-F, R_9 β-CH_3, R_{10} α-OH ist, R_{13} und R_{15} =O sind und R_{23} $-OP(O)-(OH)_2$ ist;

R_{24} C, eine C_1-C_2-Doppelbindung, O ist;
R_{25} $C(R_{15})CH_2-R_{23}$, OH, OR_{26}, $OC(=O)R_{27}$, R_{26}, COOH, $C(=O)OR_{26}$, $CHOHCH_2OH$, $CHOHCH_2OR_{26}$, $CHOHCH_2OC(=O)R_{27}$, CH_2CH_2OH, $CH_2CH_2OR_{26}$, $CH_2CH_2OC(=O)R_{27}$, CH_2CN, CH_2N_3, CH_2NH_2, CH_2NHR_{26}, $CH_2N(R_{26})_2$, CH_2OH, CH_2OR_{26}, $CH_2O(C=O)R_{27}$, $CH_2O(P=O)(OH)_2$, $CH_2O(P=O)(OR_{26})_2$, CH_2SH, CH_2S-R_{26}, $CH_2SC(=O)R_{27}$, $CH_2NC(=O)R_{27}$, $C(=O)CHR_{28}OH$, $C(=O)CHR_{28}OR_{26}$, $C(=O)CHR_{28}OC(=O)R_{27}$ ist oder
R_{10} und R_{25} zusammen $=C(R_{28})_2$ sein können, d.h. eine gegebenenfalls alkylsubstituierte Methylengruppe;

wobei R_{26} C_1-C_6-(Alkyl, verzweigtes Alkyl, Cycloalkyl, Halogenalkyl, Aralkyl, Aryl) ist;
$R_{27} = R_{26} + OR_{26}$; R_{28} = H, C_1-C_6-(Alkyl, verzweigtes Alkyl, Cycloalkyl).

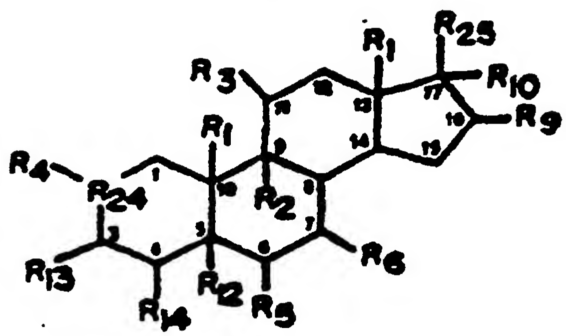
3. Verwendung nach Anspruch 2, wobei die Verbindung ausgewählt wird aus der Gruppe bestehend aus 21-Methyl-5β-pregnan-3α,11β,17α-21-tetrol-20-on-21-methylether; 3β-Azido-21-acetoxy-5β-pregnan-11β,17α-diol-20-on; 3β-Acetamido-21-acetoxy-5β-pregnan-11β,17α-diol-20-on; 5β-Pregnan-11β,17α,21-triol-20-on; 4,9(11)-Pregnadien-17α,21-diol-3,20-dion-21-acetat und 4,9(11)-Pregnadien-17α,21-diol-3,20-dion.

4. Verwendung nach Anspruch 3, wobei die Verbindung ausgewählt ist aus der Gruppe bestehend aus 4,9(11)-Pregnadien-17α,21-diol-3,20-dion-21-acetat und 4,9(11)-Pregnadien-17α,21-diol-3,20-dion.

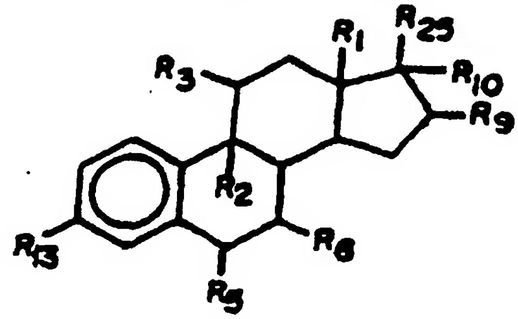
Revendications

1. Utilisation d'un agent angiostatique pour la fabrication d'un médicament pour le traitement du glaucome GLC1A.

2. Utilisation suivant la revendication 1, dans laquelle l'agent angiostatique a la structure suivante :



Structure [A]



Structure [B]

formules dans lesquelles :

R_1 est H, β-CH_3 ou β-C_2H_5;
R_2 est F, une double liaison en C_9-C_{11}, un groupe époxy en C_9-C_{11}, H ou Cl;
R_3 est H, OR_{26}, $OC(=O)R_{27}$, halogène, une double liaison en C_9-C_{11}, un groupe époxy en C_9-C_{11}, =O, -OH, -O-alkyle(C_1-C_{12}), -OC(=O)alkyle(C_1-C_{12}), OC(=O)ARYLE, -OC(=O)N(R)$_2$ ou -OC(=O)OR_7, où ARYLE est un groupe furyle, thiényle, pyrrolyle ou pyridyle et chacun desdits fragments est éventuellement substitué par un ou deux groupes alkyle en (C_1-C_4), ou bien ARYLE est un groupe -$(CH_2)_f$-phényle, dans lequel f vaut de 0 à 2 et le noyau phényle est éventuellement substitué par 1 à 3 groupes choisis parmi le chlore, le fluor, le brome et les groupes alkyle(C_1-C_3), alcoxy(C_1-C_3), thioalcoxy(C_1-C_3), Cl_3C-, F_3C-, -NH_2 et -$NHCOCH_3$ et R est de l'hydrogène, un groupe alkyle(C_1-C_4) ou un groupe phényle et chaque R peut être identique ou différent, et R_7 est un groupe ARYLE tel que défini ici ou alkyle(C_1-C_{12});
R_4 est H, CH_3, Cl ou F;
R_5 est H, OH, F, Cl, Br, CH_3, phényle, vinyle ou allyle;
R_6 est H ou CH_3;
R_9 est $CH_2CH_2OR_{26}$, $CH_2CH_2OC(=O)R_{27}$, H, OH, CH_3, F, =CH_2, $CH_2C(=O)OR_{28}$, OR_{26}, $O(C=O)R_{27}$ ou $O(C=O)CH_2(C=O)OR_{26}$;
R_{10} est -C≡CH, -CH=CH_2, halogène, CN, N_3, OR_{26}, $OC(=O)R_{27}$, H, OH, CH_3 ou bien R_{10} forme une seconde liaison entre les positions C-16 et C-17;
R_{12} est H ou forme une double liaison avec R_1 ou R_{14};
R_{13} est un halogène, OR_{26}, $OC(=O)R_{27}$, NH_2, NHR_{26}, $NHC(=O)R_{27}$, $N(R_{26})_2$, $NC(=O)R_{27}$, N_3, H, -OH, =O, -O-P(=O)$(OH)_2$ ou -O-C(=O)-$(CH_2)_t$COOH où t est un nombre entier de 2 à 6;
R_{14} est H ou forme une double liaison avec R_{12};
R_{15} est H, =O ou -OH;
et R_{23} avec R_{10} forment un phosphate cyclique;
dans lesquelles R_9 et R_{15} ont la signification donnée précédemment;
ou dans lesquelles R_{23} est OH, O-C(=O)-R_{11}, -OP(O)-$(OH)_2$ ou -O-C(=O)-$(CH_2)_t$COOH où t est un nombre entier de 2 à 6; et R_{11} est -Y-$(CH_2)_n$-X-$(CH_2)_m$-SO_3H, -Y'-$(CH_2)_p$-X'-$(CH_2)_q$-$NR_{16}R_{17}$ ou -Z$(CH_2)_r$Q,
où Y est une liaison ou -O-; Y' est une liaison, -O- ou -S-; chacun des X et X' est une liaison, -CON(R_{18})-, -N(R_{18})CO-, -O-, -S-, -S(O)- ou -S(O_2)-; R_{18} est de l'hydrogène ou un alkyle(C_1-C_4); chacun des R_{16} et R_{17} est un groupe alkyle inférieur de 1 à 4 atomes de carbone éventuellement substitué par un hydroxyle ou bien R_{16} et R_{17} pris ensemble avec l'atome d'azote auquel chacun est attaché forment un hétérocycle monocyclique choisi parmi les groupes pyrrolidono, pipéridino, morpholino, thiomorpholino, pipérazino et N(alkyl inférieur)-pipérazino dans lequel le groupe alkyle comporte de 1 à 4 atomes de carbone; n est un nombre entier de 4 à 9; m est un nombre entier de 1 à 5; p est un nombre entier de 2 à 9; q est un nombre entier de 1 à 5; Z est une liaison ou -O-; r est un nombre entier de 2 à 9; et Q est un des groupes suivants :

(1) -R_{19}-CH_2COOH dans lequel R_{19} est un groupe -S-, -S(O)-, -S(O)$_2$-, -$SO_2N(R_{20})$- ou -$N(R_{20})SO_2$-; et

R_{20} est de l'hydrogène ou un groupe alkyle(C_1-C_4); à la condition que le nombre total d'atomes de carbone dans R_{20} et $(CH_2)_r$ ne soit pas supérieur à 10; ou
(2) -CO-COOH; ou
(3) $CON(R_{21})CH(R_{22})COOH$ dans lequel R_{21} est H et R_{22} est H, CH_3, $-CH_2COOH$, $-CH_2CH_2COOH$, $-CH_2OH$, $-CH_2SH$, $-CH_2CH_2SCH_3$ ou $-CH_2Ph-OH$ où Ph-OH est du p-hydroxyphényle;

ou R_{21} est CH_3 et R_{22} est H;

ou R_{21} et R_{22} pris ensemble sont $-CH_2CH_2CH_2-$;

ou $-N(R_{21})CH(R_{22})COOH$ pris ensemble est $-NHCH_2CONHCH_2COOH$; et les sels pharmaceutiquement acceptables de ceux-ci;

à la condition que si R_{23} est un phosphate, il doit former un phosphate cyclique, avec R_{10} lorsque R_{13} est =O, à l'exception du composé dans lequel R_1 est β-CH_3, R_2 et R_3 pris ensemble forment une double liaison entre les positions 9 et 11, R_4 et R_6 sont de l'hydrogène, R_{12} et R_{14} pris ensemble forment une double liaison entre les positions 4 et 5, R_5 est α-F, R_9 est β-CH_3, R_{10} est α-OH, R_{13} et R_{14} sont =O et R_{23} est $-OP(O)-(OH)_2$.

R_{24} = C, double liaison en C_1-C_2, O;
R_{25} = $C(R_{15})CH_2$-R_{23}, OH, OR_{26}, $OC(=O)R_{27}$, R_{26}, COOH, $C(=O)OR_{26}$, $CHOHCH_2OH$, $CHOHCH_2OR_{26}$, $CHOHCH_2OC(=O)R_{27}$, CH_2CH_2OH, $CH_2CH_2OR_{26}$, $CH_2CH_2OC(=O)R_{27}$, CH_2CN, CH_2N_3, CH_2NH_2, CH_2NHR_{26}, $CH_2N(R_{26})$, CH_2OH, CH_2OR_{26}, $CH_2O(C=O)R_{27}$, $CH_2O(P=O)(OH)_2$, $CH_2O(P=O)(OR_{26})_2$, CH_2SH, CH_2S-R_{26}, $CH_2SC(=O)R_{27}$, $CH_2NC(=O)R_{27}$, $C(=O)CHR_{28}OH$, $C(=O)CHR_{28}OR_{26}$, $C(=O)CHR_{28}OC(=O)R_{27}$ ou bien R_{10} et R_{25} pris ensemble peuvent être $=C(R_{28})_2$, c'est-à-dire un groupe méthylène éventuellement substitué par alkyle;

où R_{26} = C_1-C_6(alkyle, alkyle ramifié, cycloalkyle, haloalkyle, aralkyle, aryle);
R_{27} = R_{26} + OR_{26}; R_{28} = H, C_1-C_6(alkyle, alkyle ramifié, cycloalkyle).

3. Utilisation suivant la revendication 2, dans laquelle le composé est choisi dans le groupe comprenant la 21-méthyl-5β-pregnane-3α,11β,17α,21-tétrol-20-one-21-éther méthylique, la 3β-azido-21-acétoxy-5β-pregnane-11β,17α-diol-20-one, la 3β-acétamido-21-acétoxy-5β-pregnane-11β,17α-diol-20-one, la 5β-pregnane-11β,17α,21-triol-20-one, le 4,9(11)-pregnadiène-17α,21-diol-3,20-dione-21-acétate et la 4,9(11)-pregnadiène-17α,21-diol-3,20-dione.

4. Utilisation suivant la revendication 3, dans laquelle le composé est choisi dans le groupe comprenant le 4,9(11)-pregnadiène-17α,21-diol-3,20-dione-21-acétate et la 4,9(11)-pregnadiène-17α,21-diol-3,20-dione.